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(56) Documents Cited
Febs Lett., 1993, Vol. 334 (1), pages 117-120
Tetrahedron, 1993, Vol. 49 (1), pages 1-12

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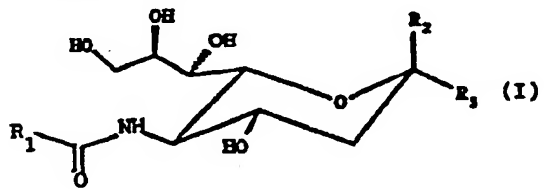
(54) Angiogenesis inhibiting sialic acid derivatives and process for their preparation

(57) Compounds of formula (I):



(I)

[wherein

R_1 is a substituent chosen from: a vinyl group unsubstituted or substituted at 1-position by a halogen atom; an oxiran ring unsubstituted or substituted at 2-or 3-position by a C_1-C_4 alkyl group; a N-aziridinyl or cyclopropyl ring; and a 4-[N,N-bis(2-haloethyl)amino]phenyl group;

one of R_2 and R_3, independently, is hydroxy or C_1-C_4 alkoxy unsubstituted or substituted by phenyl, and the other is a -COOR group wherein R is hydrogen or C_1-C_4 unsubstituted or substituted by phenyl; and the pharmaceutically acceptable salts thereof]

are angiogenesis inhibitors, ie suppress the growth of new blood vessels and are therefore useful in the treatment of chronic inflammation, diabetic retinopathy, psoriasis, rheumatoid arthritis and tumour growth.

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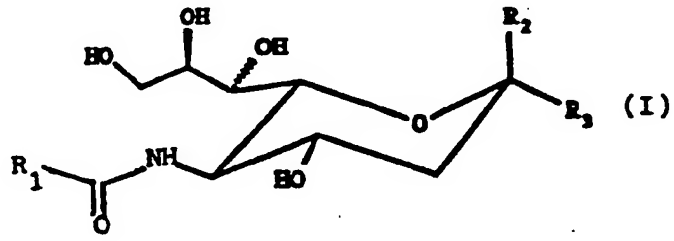
"SIALIC ACID DERIVATIVES AND PROCESS FOR THEIR PREPARATION"

The present invention relates to new N-acylneuraminic acid derivatives, to a process for their preparation, to a pharmaceutical composition containing them and to their use in therapy.

The present invention provides new derivatives of neuraminic acid having the following general formula (I)



(I)

wherein

R_1 is a substituent chosen from: a vinyl group unsubstituted or substituted at 1-position by a halogen atom; an oxiran ring unsubstituted or substituted at 2- or 3-position by a C_1-C_4 alkyl group; a N-aziridinyl or cyclopropyl ring; and a 4-/N,N-bis(2-haloethyl)amino/phenyl group;

one of R_2 and R_3, independently, is hydroxy or C_1-C_4 alkoxy unsubstituted or substituted by phenyl, and the other is a -COOR group wherein R is hydrogen or C_1-C_4 alkyl unsubstituted or substituted by phenyl; and the pharmaceutically acceptable salts thereof.

An alkyl or alkoxy group may be a branched or straight chain alkyl or alkoxy group, respectively.

A C_1-C_4 alkyl group is preferably methyl, ethyl, propyl or isopropyl, in particular methyl.

A C_1-C_4 alkoxy group is e.g. methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy or t-butoxy, in particular methoxy and ethoxy, especially methoxy.

A C_1-C_4 alkyl group substituted by phenyl is e.g. benzyl or phenethyl in particular benzyl.

A C_1-C_4 alkoxy group substituted by phenyl is e.g. a benzyloxy or phenyl-ethoxy group in particular benzyloxy.

A vinyl group substituted by halogen is e.g. a 1-chloro-vinyl or 1-bromovinyl group, in particular 1-bromovinyl.

A haloethyl group is e.g. a 2-chloroethyl, 2-bromoethyl or 2-fluoroethyl group, in particular a 2-chloroethyl group.

As already said, the invention includes within its scope also the pharmaceutically acceptable salts of the compounds of formula (I).

Examples of pharmaceutically acceptable salts are either those with inorganic bases, such as sodium, potassium, calcium and aluminium hydroxides, or with organic bases, such as lysine, arginine, N-methyl-glucamine, triethylamine, triethanolamine, dibenzylamine, methylbenzylamine, di-(2-ethylhexyl)amine, piperidine, N-ethylpiperidine, N,N-diethyl-aminoethylamine, N-ethylmorpholine, ß-phenethylamine, N-benzyl-ß-phenethylamine, N-benzyl-N,N-dimethylamine and other acceptable organic amines.

The present invention also includes within its scope pharmaceutically acceptable bioprecursors (otherwise known as prodrugs) of the compounds of formula (I), i.e. compounds which have a different formula to formula (I) above, but which nevertheless upon administration to a human being are converted directly or indirectly in vivo into a compound of formula (I). Object of the present invention are also all the possible isomers of the compounds of formula (I) either as a single isomer and as mixtures thereof.

Preferred compounds according to the present invention are the compounds of formula (I), wherein

R_1 is a 1-bromovinyl, oxiranyl or 4-/N,N-bis-(2-chloroethyl)-amino/-phenyl group;

one of R_2 and R_3 is, independently, hydroxy or methoxy and the other is a -COOR group wherein R is hydrogen or C_1-C_4 alkyl; and the pharmaceutically acceptable salts thereof.

Specific examples of the preferred compounds under this invention are the following:

Methyl ß-ketoside of 5-(α-bromoacryloyl)amino-3,5-dideoxy-D-glycero-D-galacto-nonulosonic acid methyl ester;

Methyl ß-ketoside of 5-(α-bromoacryloyl)amino-3,5-dideoxy-D-glycero-D-galacto-nonulosonic acid;

5-(α-bromoacryloyl)amino-3,5-dideoxy-D-glycero-D-galacto-nonulosonic acid;

Methyl ß-ketoside of 5-(2,3-epoxypropionyl)amino-3,5-dideoxy--D-glycero-D-galacto-nonulosonic acid methyl ester;

Methyl ß-ketoside of 5-(2,3-epoxypropionyl)amino-3,5-dideoxy--D-glycero-D-galacto-nonulosonic acid;

5-(2,3-epoxypropionyl)amino-3,5-dideoxy-D-glycero-D-galacto--nonulosonic acid;

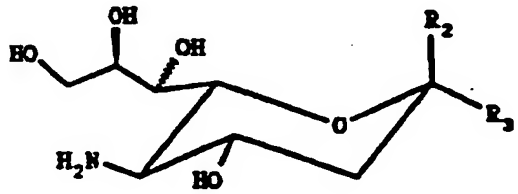
Methyl ß-ketoside of 5-/4-/N,N-bis-(2-chloroethyl)-amino/benzoyl/-amino-3,5-dideoxy-D-glycero-D-galacto-nonulosonic acid methyl ester;

Methyl ß-ketoside of 5-/4-/N,N-bis-(2-chloroethyl)-amino/benzoyl/-amino-3,5-dideoxy-D-glycero-D-galacto-nonulosonic acid;

5-/4-/N,N-bis-(2-chloroethyl)-amino/benzoyl/-amino-3,5-dideoxy--D-glycero-D-galacto-nonulosonic acid;

and the pharmaceutically acceptable salts thereof.

The compounds of the present invention and the salts thereof can be obtained by a process comprising acylating a compound of formula (II)



(II)

wherein R_2 and R_3 are as defined above, with a compound of formula (III)

$$R_1\text{-}X \qquad \text{(III)}$$

wherein

X is a reactive derivative of a carboxy group, and

R_1 is as defined above, and/or, if desired, converting a compound of formula (I) into another compound of formula (I), and, if desired, separating a mixture of stereoisomers of a compound of formula (I) into the single isomers, and, if desired, salifying a compound of formula(I) with a pharmaceutically acceptable base.

A reactive derivative of a carboxy group is for instance an L-CO- group, wherein L is a leaving group e.g. halogen, in particular chlorine or bromine, or an imidazolyl, pivaloyloxy, p-nitrophenoxy or trichlorophenoxy group; or a R_1'-CO-O group, wherein R_1', being the same as R_1, has the same values of R_1 as defined above.

The reaction between a compound of formula (II) and a compound of formula (III) is preferably carried out in the presence of a solvent and, preferably, using an excess of the compound of formula (III) in ratio of about from 1.1 to about 10 moles of compound of formula (III) to 1 mole of compound of formula (II). The solvent is, preferably, an inert organic solvent chosen e.g. from dialkylsulphoxides such as dimethylsulphoxide, dialkylamides such as dimethylformamide, heterocyclic amines such as pyridine, dioxane, tetrahydrofuran, and lower aliphatic e.g. C_1-C_4 alcohols, or water.

A particularly preferred solvent is methanol. The reaction temperature may range from about -20°C to about 25°C. The time required for the reaction may vary approximately within

about about
a range from/0.5 to/24 h.

The compounds of formula (I) prepared according to the above described procedures can be purified by conventional methods such as silica gel, alumina or ion exchange column chromatography and/or by reerystallization from organic solvents such as ethyl ether or aliphatic alcohols.

The optional conversion of a compound of formula (I) into another compound of formula (I), the optional salification of a compound of formula (I) and the optional preparation of a free compound from a salt can be carried out according to known methods.

Fractional crystallization and chromatography, used for separating a mixture of isomers of a compound of formula (I) into single isomers, can be carried out by conventional procedures.

For example, the optional conversion of a compound of formula (I) wherein R_1 is an oxirane ring, R_2 is a C_1-C_4 alkoxy, unsubstituted or substituted by a phenyl and R_3 is a -COOR group wherein R is C_1-C_4 alkoxy, into another compound of formula (I) wherein R_1, R_2 are as defined above and R_3 is free carboxy, can be performed by saponification with an alkaline base such as sodium hydroxide or lithium hydroxide in methanol/water, at room temperature as known from the art.

The compounds of formula (II) can be obtained by N-deacetylation of compounds that can be prepared according to methods described in literature (J. Biol. Chem., 244, 1306, 1969). The compounds of formula (III) are known compounds also and they can be

prepared through activation of the carboxy parent compounds in a conventional way.

PHARMACOLOGY

The compounds of the invention have been found to be active as angiogenesis inhibitors.

By angiogenesis inhibitor is meant an agent capable of suppressing the growth of new blood vessels. Therefore the compounds of the present invention are useful in treating several pathological conditions in mammals, including humans, where the growth of new blood vessels is detrimental, for example in chronic inflammation, diabetic retinopathy, psoriasis, rheumatoid arthritis and tumor growth. In particular, in cancer therapy the compounds of the invention can be administered alone or in a combined method of treatment with antitumor agents such as cytarabine, methotrexate, aminopterin sodium, daunomycin, actinomycin D, chloroambucyl, cisplatin, tamoxifen, 8-azaguanine, doxorubicin, etoposide, fluorouracil, melphalan, cyclophosphamide, bleomycin, vinblastin or mitomycin. The term "combined" method of treatment is meant to include both separate and substantially contemporaneous administration of a pharmaceutical composition containing a therapeutically effective amount of a compound according to the invention and a pharmaceutical composition containing a different pharmaceutically active agent.

Accordingly the present invention provides also products containing an antitumor agent and a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof as a combined preparation for simultaneous, separate or sequential use in cancer therapy.

The angiogenesis inhibitor activity of the compounds of the present invention is shown e.g. by the fact that they have been found to be active in the chorioallantoic membrane test, according to the Folkman's method: Nature, 279, 307 (1982). The compounds of the invention can be administered by the usual routes, for example, parenterally, e.g. by intravenous injection or infusion, intramuscularly, subcutaneously, topically or orally. The dosage depends on the age, weight and condition of the patient and on the administration route.

For example, a suitable dosage for administration to adult humans may range from about 0.5 to about 100 mg pro dose 1-4 times a day.

The pharmaceutical compositions of the invention may contain a compound of formula (I) or a pharmaceutically acceptable salt thereof as the active substance, in association with one or more pharmaceutically acceptable excipients and/or carriers.

The pharmaceutical compositions of the invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form.

For instance, solutions for intravenous injection or infusion may contain as carrier, for example, sterile water or preferably, they may be in the form of sterile aqueous isotonic saline solutions.

Suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride.

In formulations for topical application, e.g. creams, lotions or pastes for use in dermatological treatment, the active ingredient may be mixed with conventional oleaginous or emulsifying excipients.

The solid oral forms, e.g. tablets and capsules, may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch and potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethyl cellulose, polyvinylpyrrolidone; disaggregating agents, e.g. a starch, alginic acid, alginates, sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, for instance, lecithin, polysorbates, laurylsulphates: and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in a known

manner, for example by means of mixing, granulating, tabletting, sugar-coating, or film-coating processes.

Furthermore, according to the invention there is provided a method for treating pathological conditions where the growth of new blood vessels is detrimental, for example chronic inflammation, diabetic retinopathy, psoriasis, rheumatoid and arthritis and tumors, in mammals in need thereof, including humans, comprising administering to the said mammals a composition of the invention.

The following examples illustrate but do not limit the invention.

EXAMPLE 1

Methyl ß-ketoside of 5-amino-3,5-dideoxy-D-glycero-D-galacto-nonulosonic acid methyl ester hydrochloride.

Methyl ß-ketoside of acetylneuraminic acid methyl ester (1.3 g; 3.85 mmol) is dissolved in a N solution of HCl in methanol (100 mL) and kept in a sealed tube at 80°C for 20 h. The resulting mixture is then evaporated to dryness to obtain a foamy solid which can be used without further purification; yield: 1.25 g (89%).

^{1}H-NMR(DMSO-d_6) : δ = 1.55(dd,1H); 2.2(dd,1H); 2.6-4.1(m,7H); 3.2(s,3H); 3.7(s,3H); 8.2ppm(br,NH_3+).

EXAMPLE 2

Methyl ß-ketoside of 5-(α-bromoacryloyl)amino-3,5-dideoxy-D-glycero-D-galacto-nonulosonic acid methyl ester.

To a stirred and cooled (0°C) solution of α-bromoacrylic acid (2.91 g; 19.3 mmol) in EtOAc (17 mL) N,N'-dicyclohexyl-carbodiimid (2,19 g; 10.6 mmol) is added under N_2. The mixture is kept at room temperature for 2,5 h and filtered to remove any insoluble material. The clear filtrate is then added dropwise over 1 h period to a solution of methyl ß-ketoside of neuraminic acid methyl ester hydrochloride (670 mg; 1.93 mmol) in methanol (25 mL) in presence of Amberlist A 21 (3.35 g) at 5°C. The resulting mixture is kept at this temperature for 2 h, filtered and evaporated to dryness under reduced pressure. The crude product is chromatographed on silica gel with chloroform/methanol (9:1) to give the desired product as a white solid; yield: 320 mg (39%).

^{1}H-NMR (DMSO-d_6): δ = 1.5(dd,1H); 2.15(dd,1H); 2.8-4.2(m,11H); 3.17(s,3H); 3.7(s,3H); 6.2(d,1H); 6.7(d,1H); 8.27ppm(d,1H).

By analogous procedure the following compounds can be obtained:
Methyl ß-ketoside of 5-(α-bromoacryloyl)amino-3,5-dideoxy-D-glycero-D-galacto-nonulosonic acid ; ^{1}H-NMR (DMSO-d_6): δ = 1.41 (t, 1H); 2.02 (dd, 1H); 3.03 (S, 3H); 3.30-3.60 (m, 4H); 3.23 (d, 1H); 3.75 (m, 1H); 3.90 (m, 1H); 4.20 (brs, 1H); 4.60 (brs, 1H); 4.80 (brs, 1H); 5.18 (brs, 1H); 6.15 (d, 1H); 6.68 (d, 1H); 8.18 (d, 1H);
5-(α-bromoacryloyl)amino-3,5-dideoxy-D-glycero-D-galacto-nonulosonic acid;
Methyl ß-ketoside of 5-[4-[N,N-bis-(2-chloroethyl)-amino]-benzoyl]-amino-3,5-dideoxy-D-glycero-D-galacto-nonulosonic acid methyl ester ;

Methyl ß-ketoside of 5-/4-/N,N-bis-(2-chloroethyl)-amino/benzoyl/-amino-3,5-dideoxy-D-glycero-D-galacto-nonulosonic acid, and
5-/4-/N,N-bis-(2-chloroethyl)-amino/benzoyl/-amino-3,5--dideoxy-D-glycero-D-galacto-nonulosonic acid.

EXAMPLE 3

Methyl ß-ketoside of 5-(2,3-epoxypropionyl)amino-3,5-dideoxy-D-glycero-D-galacto-nonulosonic acid methyl ester.

To a stirred solution of racemic 2,3-epoxypropionic acid (1.15 g; 13.1 mmol) in EtOAc (11 mL), cooled in an ice bath, N,N'-dicyclo-hexylcarbodiimid (1.46 g; 7.23 mmol) is added under nitrogen atmosphere. The mixture is kept at room temperature for 4 h and filtered on buchner to remove the formed dicyclohexylurea. The clear filtrate is added dropwise during 1 h period to a solution of methyl ß-ketoside of nauraminic acid methyl ester hydrochloride (457 mg; 1.31 mmol) in methanol (9 mL) in presence of Amberlist A 21 (914 mg) at 5°C. The mixture is then kept at room temperature for 1 h, filtered and evaporated to dryness. The crude product is chromatographed on silica gel with chloroform/methanol (8:2) to give the desired product as a mixture of epimers; yield: 308 mg (64%).

^{1}H-NMR(DMSO-d_6) : δ =1.5(m,1H); 2.15(m,1H); 2.85(m,2H); 3.17(s,3H); 3.2-4(m,8H); 3.7(s,3H); 8.18(d,0.5H); 8.32(d,0.5H).

By analogous procedure the following compounds can be obtained:
methyl ß-ketoside of 5-(2,3-epoxypropionyl)amino-3,5-dideoxy-D-glycero-D--galacto-nonulosonic acid; ^{1H}-NMR (DMSO-d_6): δ= 1.42 (dd, 1H); 2.02 (m, 1H); 2.83 (m, 2H); 3.05 (S, 3H); 3.2-4 (m, 8H); 8.08 (d, 0.5H); 8.21 (d, 0.5H); and 5-(2,3-epoxypropionyl)amino-3,5-dideoxy-D-glycero-D-galactononulosonic acid.

EXAMPLE 4

Methyl ß-ketoside of 5-(α-bromoacryloyl)amino-3,5-dideoxy-D-glycero-D-galacto--nonulosonic acid.

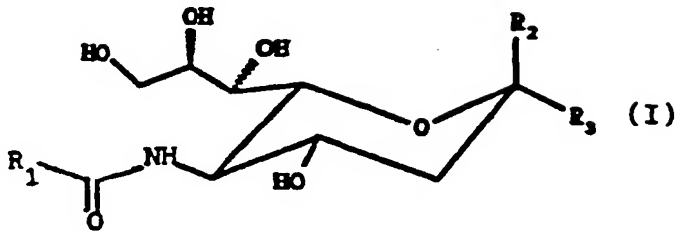
To a stirred solution of 0.1N sodium hydroxide in water (35.6 ml; 3.56 mmol) methyl ß-ketoside of 5-(α-bromoacryloyl)amino-3,5-dideoxy-D-glycero-D--galacto nonulosonic acid methyl ester (1.45 g; 3.39 mmol) is added and the mixture is stirred at room temperature for one hour. The clear solution is then neutralized with Amberlite IRC-50 (H^+) (500 mg), filtered and evaporated to dryness. The crude material is taken up with ethyl acetate, filtered and collected to give the desired product as a white solid; yield: 1.47 g (100%)
^{1}H-NMR (DMSO-d_6): δ= 1.41 (t, 1H); 2.02 (dd, 1H); 3.03 (S, 3H); 3.30-3.60 (m,4H); 3.23 (d, 1H); 3.75 (m, 1H); 3.90 (m, 1H); 4.20 (brs, 1H); 4.60 (brs, 1H); 4.80 (brs, 1H); 5.18 (brs, 1H); 6.15 (d, 1H); 6.68 (d, 1H); 8.18 (d, 1H).
By analogous procedure the following compounds can be obtained:
methyl ß-ketoside of 5-(2,3-epoxypropionyl)amino-3,5-dideoxy-D-glycero-D--galacto-nonulosonic acid; ^{1}H-NMR (DMSO-d_6): δ= 1.42 (dd, 1H); 2.02 (m, 1H); 2.83 (m, 2H); 3.05 (S, 3H); 3.2-4 (m, 8H); 8.08 (d, 0.5H); 8.21 (d, 0.5H) and methyl ß-ketoside of 5-[4-[N,N-bis-(2-chloroethyl)-amino]benzoyl]-amino-3,5--dideoxy-D-glycero-D-galacto-nonulosonic acid.

EXAMPLE 5

Intramuscular injection 40 mg/ml.
Aninjectable pharmaceutical preparation can be manufactured by dissolving 40 g of Methyl ß-ketoside of 5-(2,3-epoxypropionyl)-amino-3,5-dideoxy-D-glycero-D-galacto-nonulosonic acid methyl ester in water for injection (1000 ml) and sealing ampoules of 1-10 ml.

CLAIMS

1. A compound of formula (I)



(I)

wherein

R_1 is a substituent chosen from: a vinyl group unsubstituted or substituted at 1-position by a halogen atom; an oxiran ring unsubstituted or substituted at 2- or 3-position by a C_1-C_4 alkyl group; a N-aziridinyl or cyclopropyl ring; and a 4-/N,N-bis(2-haloethyl)amino/phenyl group;

one of R_2 and R_3, independently, is hydroxy or C_1-C_4 alkoxy unsubstituted or substituted by phenyl, and the other is a -COOR group wherein R is hydrogen or C_1-C_4 alkyl unsubstituted or substituted by phenyl; and the pharmaceutically acceptable salts thereof.

2. A compound of formula (I), according to claim 1, wherein

R_1 is a 1-bromovinyl, oxiranyl or 4-/N,N-bis-(2-chloroethyl)-amino/-phenyl group;

one of R_2 and R_3 is, independently, hydroxy or methoxy and the other is a -COOR group wherein R is hydrogen or C_1-C_4 alkyl; and the pharmaceutically acceptable salts thereof.

3. A compound selected from the group consisting of:

Methyl ß-ketoside of 5-(α-bromoacryloyl)amino-3,5-dideoxy-D-glycero-D-galacto-nonulosonic acid methyl ester;

Methyl ß-ketoside of 5-(α-bromoacryloyl)amino-3,5-dideoxy-D-glycero-D-galacto-nonulosonic acid;

5-(α-bromoacryloyl)amino-3,5-dideoxy-D-glycero-D-galacto-nonulosonic acid;

Methyl ß-ketoside of 5-(2,3-epoxypropionyl)amino-3,5-dideoxy--D-glycero-D-galacto-nonulosonic acid methyl ester;

Methyl ß-ketoside of 5-(2,3-epoxypropionyl)amino-3,5-dideoxy--D-glycero-D-galacto-nonulosonic acid;

5-(2,3-epoxypropionyl)amino-3,5-dideoxy-D-glycero-D-galacto--nonulosonic acid;

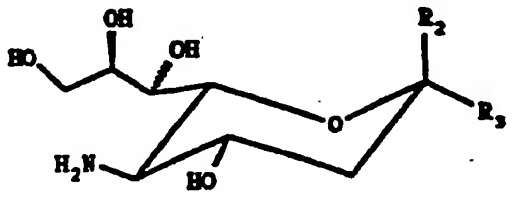
Methyl ß-ketoside of 5-/4-/N,N-bis-(2-chloroethyl)-amino/benzoyl/-amino-3,5-dideoxy-D-glycero-D-galacto-nonulosonic acid methyl ester;

Methyl ß-ketoside of 5-/4-/N,N-bis-(2-chloroethyl)-amino/benzoyl/-amino-3,5-dideoxy-D-glycero-D-galacto-nonulosonic acid;

5-/4-/N,N-bis-(2-chloroethyl)-amino/benzoyl/-amino-3,5-dideoxy-D-glycero-D-galacto-nonulosonic acid;

and the pharmaceutically acceptable salts thereof.

4. A process for the preparation of a compound of formula (I) and a pharmaceutically acceptable salt thereof, the process comprising acylating a compound of formula (II)



(II)

wherein R_2 and R_3 are as defined above, with a compound of formula (III)

$$R_1\text{-}X \qquad \text{(III)}$$

wherein

X is a reactive derivative of a carboxy group, and

R_1 is as defined above, and/or, if desired, converting a compound of formula (I) into another compound of formula (I), and, if desired, separating a mixture of stereoisomers of a compound of formula (I) into the single isomers, and, if desired, salifying a compound of formula(I) with a pharmaceutically acceptable base.

5. A product containing an antitumor agent and a compound of formula (I), according to claim 1, or a pharmaceutically acceptable salt thereof as a combined preparation for simultaneous, separate or sequential use in cancer therapy.

6. A pharmaceutical composition containing a suitable carrier and/or diluent and; as an active principle, a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof.

7. A compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof for use as an angiogenesis inhibitor.

8. A process for the preparation of a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof, said process being substantially as hereinbefore described in any one of Examples 1 to 4.

9. A pharmaceutical composition substantially as hereinbefore described in Example 5.

Patents Act 1977 18 Examiner's report to the Comptroller under Section 17 (The Search report)	Application number GB 9409395.2
Relevant Technical Fields (i) UK Cl (Ed.N) C2C (CKM, CKN) (ii) Int Cl (Ed.6) C07D	Search Examiner MR S QUICK Date of completion of Search 21 JULY 1995
Databases (see below) (i) UK Patent Office collections of GB, EP, WO and US patent specifications. (ii) ONLINE: CAS ONLINE	Documents considered relevant following a search in respect of Claims :- 1-9

Categories of documents

X:	Document indicating lack of novelty or of inventive step.	**P:**	Document published on or after the declared priority date but before the filing date of the present application.
Y:	Document indicating lack of inventive step if combined with one or more other documents of the same category.	**E:**	Patent document published on or after, but with priority date earlier than, the filing date of the present application.
A:	Document indicating technological background and/or state of the art.	**&:**	Member of the same patent family; corresponding document.

Category	Identity of document and relevant passages	Relevant to claim(s)
X	Febs Lett; 1993, volume 334 (1), pages 117-120, see especially highlighted passages	1-4 and 8
X	Tetrahedron; 1993, volume 49 (1), pages 1-12, see especially highlighted passages	1-4 and 8

Databases: The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).